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Cell adhesion receptors – signaling capacity and exploitation by bacterial pathogens

Abstract Cell adhesion receptors play an essential role in multicellular organisms by mediating the direct association of cells with each other and with proteins of the extracellular matrix. Members of different protein families such as integrins, cadherins, immunoglobulin superfamily cell adhesion molecules (IgCAMs), selectins, and syndecans not only support the structural integrity of cells and tissues, but also contribute to the transduction of signals. Interestingly, several of these molecules are exploited by bacterial pathogens to establish tight contact with eukaryotic cells. Using the example of integrins, cadherins, and IgCAMs, this review illustrates the signaling capacity of cell adhesion receptors and highlights a number of bacterial adhesins that are known to engage these receptors. Where applicable, the role of the receptor-adhesin interaction in the course of the infection is discussed.

Keywords Pathogenic bacteria · Adhesion receptors · Signal transduction · Invasion

Introduction

The complexity of multicellular organisms depends on the ability of single cells to adhere to extracellular matrix (ECM) proteins and to form tight associations with neighboring cells as a prerequisite to build cell layers, tissues and organs. Therefore, multicellular organisms express specialized surface receptors not found in prokaryotes or unicellular eukaryotes. Cell adhesion receptors can be subdivided into several groups, most importantly the integrins, the cadherins, the immunoglobulin superfamily cell adhesion molecules (IgCAMs), the selectins, and the syndecans (Fig. 1). These protein families each contain multiple members (e.g. 765 immunoglobulin superfamily members are encoded in the human genome); however, the number of different receptors can often be greatly expanded by alternative splicing. Adhesion receptors usually display specificity for particular substrates and their expression can be cell type- or development-specific. As multiple adhesion molecules from different families are found on a single cell, their combined binding specificity determines the adhesive properties of a given cell.

Investigations over the last decade have demonstrated that in addition to their structural role, adhesion receptors in most cases also engage in signal transduction from the exterior to the interior of the cell. Due to these multiple functions, the presence of adhesion receptors can be critical for the organism and is best demonstrated by the sometimes fatal or severe phenotypes caused by deletion or mutation of the respective genes [30]. As a result, there has to be a strong selection pressure on multicellular organisms to maintain the integrity of these proteins. At the same time, their surface exposure, their signaling capacity, and their conservation make them ideal targets for pathogens trying to anchor themselves to or to communicate with host cells. Indeed, progress at the cellular level of infectious diseases now provides numerous examples of microorganisms that recognize cell adhesion receptors and exploit their function for their own purpose. In this review, the signaling functions of several mammalian cell adhesion receptors are summarized from an infectious biology point of view, integrating the molecular knowledge about the bacterial adhesins employed by distinct pathogens. In particular, this review focuses on members of the integrin, cadherin and IgCAM families as well as on associated signaling molecules. In addition, the potential role that the adhesin-receptor interaction might play during the course of the infection is discussed.

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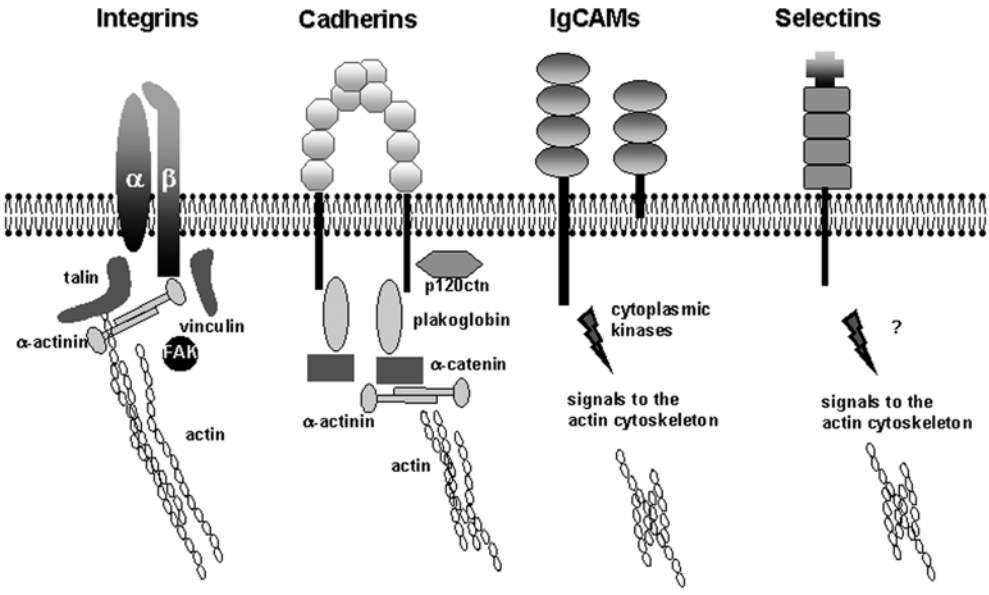

Fig. 1. Major classes of cell adhesion molecules and their connections to the actin cytoskeleton

Integrins

Integrins are cell surface glycoproteins that bind to ECM proteins or recognize membrane-bound counter receptors. As heterodimeric receptors they consist of one α and one β subunit, both containing a large extracellular domain, a single transmembrane stretch and, with the exception of integrin $\beta 4$, a short cytoplasmic tail. In mammals, there are 19 distinct α subunits and 8 β subunits that are combined into 25 receptors, where the ligand-binding ability is dependent on both subunits [29, 61]. Whereas some integrins seem to be specific for a single ligand, others recognize several ECM proteins, and, while integrin-ligand interaction can depend on a short recognition sequence within the ligand (e.g. the RGD motif in the ECM protein fibronectin that is recognized by integrin $\alpha_5\beta_1$), other integrins recognize the overall conformation of the ligand [17]. Interestingly, the affinity of the integrin for its ligand can be altered by signals from within the cell (inside-out signaling) in a process referred to as integrin activation [28]. Therefore, not only can a cell modulate the type and number of integrins expressed on its surface, the activation state of the surface-exposed integrins can be altered, allowing flexibility in the specificity and strength of adhesive contact. An additional layer of complexity is due to the fact that cells often express multiple integrins with sometimes overlapping and/or redundant adhesive properties.

In adherent cells, integrins are usually clustered at cell attachment sites called focal adhesions. At these sites, the integrins not only anchor cells to the ECM via their extracellular domains, but also integrate, via their cytoplasmic domains, the attachment on the outside of the cell with the organization of the intracellular actin cytoskeleton (hence the name integrins). Therefore, integrin-rich attachment sites are the focal origins of thick actin bundles within the cell, the so-called actin stress fibers, that control cell shape and tension.

In addition to their structural function, integrin-rich focal adhesion sites are centers for the transduction of extracellular signals into the cell (outside-in-signaling) involved in multiple cellular processes most importantly adhesion-dependent cell survival, proliferation and cell motility [16, 52]. In line with this signaling role, integrins at focal adhesions associate with cellular signaling molecules. The most prominent signaling molecule enriched at focal adhesions is the focal adhesion kinase (FAK), a non-receptor tyrosine kinase.

Focal adhesion kinase as an integrin-associated signaling molecule

Focal adhesion kinase (FAK) together with Pyk2 form a subfamily of FAK-like protein-tyrosine kinases (PTKs) (reviewed in [51]). FAK-like kinases have been detected in man, mouse, chicken, frog and fruit fly with a strong conservation of the overall domain structure. The N-terminal region harbors a FERM (band four point one-ezrin-radixin-moesin) homology domain allowing FAK association with other PTKs and ezrin. Based on the moesin crystal structure, the FERM domain is subdivided into three lobes containing binding modules that either in combination or individually enable FAK to recognize other proteins. The C-terminal region of FAK encompasses two proline-rich motifs (amino acids 712–723 and 867–882), that serve as binding sites for the adapter molecule $p130^{CAS}$, and the Rho GTPase-activating protein (GAP) GRAF or the Arf GAP ASAPI. The C-terminal FAK region also contains the focal adhesion targeting or F.A.T. domain that spans binding sites for talin and paxillin (reviewed in [47]).

Regulation of FAK activation and downstream signaling events

FAK activity and its tyrosine phosphorylation are up-regulated in response to cell-matrix contact, a number of soluble cellular activators, as well as mechanical stress (reviewed in [51]). However, we know surprisingly little about the molecular mechanisms that underlie FAK tyrosine kinase activation. A number of studies have shown that FAK activation and autophosphorylation at tyrosine-397 (Y-397) result in the recruitment of Src-like PTKs. The signaling complex formed between FAK and c-Src leads to Src-mediated FAK phosphorylation at Y-407, Y-576, Y-577, Y-861, and Y-925. FAK is also highly serine phosphorylated in the C-terminal domain, which is regulated during the cell cycle and may promote $p130^{CAS}$ dissociation.

Signals from the FAK/Src complex enhance and prolong activation of ERK/MAP kinases in cells plated on integrin ligands [51]. Recent studies show that FAK also contributes to growth factor-initiated MAP kinase activation [24]. Although it is not clear how FAK enhances growth factor-dependent signals, it has been speculated that the FERM domain-mediated association of FAK with activated growth factor receptors may contribute to this signaling connection. Additionally, FAK is also involved in integrin- and growth factor-initiated activation of JNK/SAP kinases [2, 25]. A possible link between FAK activation and SAP kinase stimulation is the tripartite complex formed between FAK, Src and $p130^{CAS}$. Tyrosine phosphorylation of $p130^{CAS}$ promotes Crk adapter molecule binding and the coordination of signals leading to the small GTPase Rac and to JNK/SAP kinase [12]. Supporting this hypothesis, a FAK/$p130^{CAS}$ complex activates JNK in response to fibronectin stimulation of primary fibroblasts, and disruption of the FAK/Src/$p130^{CAS}$ complex in human A549 epithelial cells impairs EGF-stimulated JNK activation [25].

Recent findings suggest that the FAK/Src complex makes additional connections to small GTPases. The N-terminal LD4 motif of the FAK-associated protein paxillin binds to the adapter protein p95PKL/GIT1 that associates with the guanine nucleotide exchange factors for Rac and Cdc42 of the Cool/PIX family [58]. A direct interaction of FAK and GIT1 has been reported [63] that may involve Cool/PIX recruitment to focal adhesions and subsequent stimulation of Rho-like GTPases Rac and Cdc42. Additional connections between FAK and Rho GTPases exist, as FAK-deficient cells exhibit elevated Rho activity that is repressed upon FAK re-expression. Since the FAK-associated Rho GAP GRAF could represent a negative regulator of Rho GTPases, it is possible that FAK modulates Rho activity via the recruitment and activation of GRAF. The local stimulation of Rac and Cdc42 and down-modulation of Rho by FAK-coordinated protein complexes may be an important linkage to the dynamic regulation of the actin cytoskeleton. In addition to effects on signaling cascades, FAK can also phosphorylate focal contact- and actin-associated molecules like paxillin or α-actinin [33]. It is exciting to speculate that FAK exerts a direct regulatory function on focal contacts and the actin cytoskeleton through tyrosine phosphorylation of key molecules.

Pathogenic bacteria engaging integrins

The classic examples of pathogens binding to integrins on the cell surface are found in the genus *Yersinia*. The enteropathogenic species *Y. pseudotuberculosis* and *Y. enterocolitica* express an outer membrane protein that functions as a ligand for β1 integrins. This *Yersinia* adhesin has been termed invasin, since its expression allows the bacteria not only to bind to, but also to invade into integrin β1-expressing cells [31]. Thus, attachment of invasin-positive bacteria (or even invasin-coated particles) triggers an internalization process resulting in membrane-surrounded, intracellular bacteria. Interestingly, structural analysis has revealed a striking similarity between invasin and fibronectin, a physiological ligand of β1 integrins [32]. Indeed, both molecules seem to bind to the same region of $\alpha5\beta1$ as suggested by competitive inhibition experiments and mutational analysis. The structural homology comes as a surprise, since there is no sequence similarity between these two β1 integrin-binding proteins implying a convergent evolution. Uptake of invasin-expressing bacteria takes place via a zipper-like internalization mechanism, which is characterized by a circumferential binding of integrins about the surface of the bacteria. In addition to the integrin extracellular domain, the integrin β1 cytoplasmic domain, but not the α integrin cytoplasmic domain is required for bacterial internalization, suggesting that molecular connections emanating from the β1 integrin cytoplasmic domain are required.

As the FAK is an important mediator of integrin signaling, Alrutz and Isberg [3] investigated the role of FAK in the invasion process. In particular, they demonstrated that both a dominant-negative version of FAK (FRNK) and a version with mutated autophosphorylation site (FAK Y397F), when expressed in the host cell, severely inhibit the invasin-mediated uptake of bacteria. In agreement with the role of FAK Y397 in recruiting Src family kinases following FAK autophosphorylation, Src mutants interfering with endogenous Src function also block the invasin-triggered internalization of bacteria, suggesting that an integrin β1-FAK-Src signaling axis controls invasion of pathogenic *Yersinia*.

What is the role of the invasin-integrin interaction during the pathogenesis of *Y. enterocolitica* and *Y. pseudotuberculosis*? It is thought that *Yersinia* employ invasin to exit the gastrointestinal tract, where they arrived by the way of contaminated food or water, during their passage through the small intestine [1]. Although the regular enterocytes lining the small intestine do not

present β1 integrins on their apical surface directed towards the intestinal lumen, it has been demonstrated that β1 integrins are present on the luminal surface of specialized enterocytes (M-cells) covering Peyer's patches. In addition to overcoming the epithelial barrier, transcytosis through M-cells via invasin-integrin interaction allows the bacteria to directly gain access to lymph nodes of the mucosa-associated lymphoid tissue, the place of extracellular proliferation and spread of pathogenic *Yersinia*. Interestingly, *Y. pestis*, a closely related pathogen that is not transmitted by the oral route, but instead uses an insect vector for direct transfer into the host blood stream (and therefore does not need to overcome an epithelial barrier), does not express invasin protein. The lack of invasin expression is due to the disruption of the invasin gene by an IS200-like insertion sequence element [54].

Binding to β1 integrins in in vitro assays has been reported for the intimin adhesin of enteropathogenic *Escherichia coli* (EPEC) [13]. Upon contact, EPEC inserts a protein into the host cell membrane called Tir that serves as the counter receptor for the bacteria-associated intimin [35]. Interestingly, the region of Tir that is recognized by intimin seems to display homologies to integrin β1, further suggesting that intimin might also bind to certain cellular integrins [34]. However, a functional significance for the interaction between intimin and integrins in vivo is currently unknown.

Integrins have also been documented to serve as co-receptors for pathogenic *Neisseria gonorrhoeae* during syndecan-mediated uptake. In particular, binding of the gonococcal Opa_{50} adhesin (belonging to the opacity-associated or Opa protein family) to heparan sulfate proteoglycans of the syndecan family can induce internalization that is greatly enhanced by the addition of the integrin αv ligand vitronectin, and this enhancement can be blocked by specific antibodies directed against integrins $\alpha v\beta 3$ and $\alpha v\beta 5$ [11, 18]. It is fascinating that in this case the pathogen does not seem to directly bind to the integrin on human cells, but captures a physiological ligand (vitronectin) to exploit integrin function.

A similar strategy is seen in *Staphylococcus aureus*, where surface proteins (fibronectin binding proteins, FnBPs) mediate the binding of the ECM protein fibronectin, which in turn leads to recognition by the cellular fibronectin receptor, integrin $\alpha 5\beta 1$ [38, 55]. As invasion can be blocked by specific antibodies against integrin $\alpha 5\beta 1$ or cytochalasin D, *S. aureus* seems to utilize the integrin-actin cytoskeleton linkage to gain access to the interior of the cell.

Cadherins

Cadherins are transmembrane glycoproteins that mediate tight homotypic cell-cell association (for review see [57]). These receptors are expressed in a cell-type specific manner, with N-, P-, R-, B- and E- (epithelial) cadherin as prominent examples and about ten additional family members. In their extracellular part, cadherins possess five cadherin-motif subdomains that allow these receptors to dimerize with neighboring cadherin molecules in the presence of Ca^{2+} [48]. This cis-interaction of the receptors is the pre-requisite for the trans-interaction between cadherins situated within two opposing cell membranes. The trans-interaction not only tethers two cells together, but promotes the clustering of cadherins in adherence junctions, resulting in cadherin-associated complexes (CACs) on the cytoplasmic face of the membrane [44]. CACs are enriched in proteins like β-catenin, plakoglobin (γ-catenin), α-catenin, p120ctn, ZO-1, vinculin, and α-actinin that either bind directly or indirectly to the membrane receptor. In addition, these proteins link cadherin receptors to the intracellular actin cytoskeleton. Cadherin-mediated cell-cell association is not only regulated by extracellular calcium levels, but also by signals from within the cell that modulate the stability of CACs, leading to a weakening or strengthening of the cadherin clusters. It has been shown for example that phosphorylation of p120ctn and β-catenin influences cell-cell adhesion via E-cadherin.

As is true for integrins, cadherin-mediated cell-cell association not only contributes to structural and cohesive aspects of tissues, but is also intimately linked to the regulation of gene expression during development and differentiation. Studies of the morphogenic Wnt signaling pathway in *Drosophila* have revealed that a key player, the armadillo protein, is the fly homologue of β-catenin. Subsequently, it could be shown that sequence repeats in armadillo and β-catenin (the so-called armadillo repeats) are involved in the interaction between these proteins and the transcription factor LEF-1/TCF. LEF-1/β-catenin complexes can enter the nucleus and initiate transcription from specific sequences recognized by the DNA-binding domain of LEF-1 and promoted by the C-terminal domain of β-catenin, demonstrating that this initially characterized adherence junction protein also functions in gene regulation. The Wnt-cadherin signaling pathway seems to be controlled by the balance between cadherin-associated β-catenin at adherence junctions and the level of free cytoplasmic β-catenin. In addition, the level of cytoplasmic β-catenin is controlled by an interplay between the GSK3 kinase and the product of the APC tumor suppressor gene in vertebrates and the corresponding homologues in Drosophila.

Pathogenic bacteria engaging cadherins

A prominent example of pathogenic bacteria engaging cadherins is found in the genus *Listeria*. The gram-positive, facultative intracellular pathogen *Listeria monocytogenes* expresses a family of adhesins termed internalins that mediate the invasion of this pathogen into different cell types. Whereas internalin B confers invasion into a number of different cell types and seems to associate with different receptors [7, 53], internalin A

(InlA) allows the bacteria to efficiently penetrate human epithelial cells [15] and this property is based on InlA binding to human E-cadherin [39]. Interestingly, like the homophilic interaction between cadherins, the binding of InlA to E-cadherin is Ca^{2+} dependent. As cadherins are linked to the actin cytoskeleton, it is not surprising that InlA-mediated invasion can be blocked by agents that disrupt the integrity of the actin cytoskeleton such as cytochalasins. It has been puzzling for some time that, although InlA seems to be essential for *Listeria* invasion into epithelial cells in vitro, deletion of this virulence factor did not result in decreased virulence of *L. monocytogenes* in experimental infection in mice. Clearly, mice are not very susceptible to infection by *L. monocytogenes* via the oral route, whereas guinea pigs are. However, by mapping the InlA binding site in human E-cadherin and sequence comparisons with the mice and the guinea pig variant, it could be demonstrated that a single amino acid exchange at position 16 (Pro-16 in human and guinea pig E-cadherin versus Glu-16 in mouse) is decisive for the recognition by InlA [36]. Interestingly, mice expressing human E-cadherin in their intestinal epithelial cells gain susceptibility to oral infection by *L. monocytogenes*, indicating that the InlA-E-cadherin interaction is critically involved in an initial step in pathogenesis determining if the food-borne pathogen can successfully exit the small intestine to reach a permissive niche within the host [37]. As E-cadherin has a restricted subcellular distribution and localizes to the basolateral membrane in polarized epithelial cells, it is still debated how InlA might get access to E-cadherin from within the intestinal lumen. However, since the InlA adhesin in vivo does not act alone, it is conceivable that additional virulence factors of *L. monocytogenes* might aid in the exploitation of cellular E-cadherin by InlA.

Immunoglobulin superfamily cell adhesion molecules

Cell adhesion molecules of the immunoglobulin superfamily are widely distributed in eukaryotic cells and can be found on virtually every cell type. These glycoproteins are characterized by the presence of at least one immunoglobulin-like domain in their extracellular part. The immunoglobulin domain seems to be perfectly suited for binding and recognition, making this probably the reason why it is employed during evolution for the most versatile binding molecules, the immunoglobulins. IgCAMs appear as integral membrane proteins or connected to the membrane via a glycosylphosphatidylinositol (GPI) anchor. Often these receptors mediate transient cell-cell interactions. They are prominently involved in cell-cell recognition in the immune system as well as in the brain [8]. Many IgCAMs are engaged in signaling, and members of the Ig superfamily are well studied examples of signaling, most importantly the B and T cell receptors. In both cases, it is the cytoplasmic domain of the receptor or an associated co-receptor that is able to initiate an intracellular signaling cascade. Since these receptors, like integrins or cadherins, do not possess intrinsic enzymatic activities, they have to recruit and associate with cytoplasmic kinases or phosphatases. Indeed, conserved motifs have been defined in receptors of the Ig superfamily that are phosphorylated upon receptor engagement and that provide high affinity binding sites for Src homology 2 (SH2) or phosphotyrosine-binding (PTB) domain-containing proteins. For example, the B cell antigen receptor contains a so-called immunoreceptor tyrosine-based activation motif (ITAM) that upon phosphorylation by Src family protein tyrosine kinases is recognized by the SH2 domains of the cytoplasmic tyrosine kinase Syk. This in turn phosphorylates additional downstream effectors, finally leading to B cell proliferation and antibody production [50]. However, other motifs have been characterized that initiate signals resulting in down-regulation of certain cellular functions. These motifs have been termed immunoreceptor tyrosine-based inhibition motif (ITIM) and seem to be connected to the recruitment of cytoplasmic phosphatases that interfere with intracellular signaling events [5].

Pathogenic bacteria engaging IgCAMs

A prominent example of bacteria exploiting IgCAMs is found in the genus Neisseria, where pathogenic *N. gonorrhoeae* and *N. meningitidis* both express adhesins of the Opa_{52}-type that bind to members of the carcinoembryonic antigen-related cell adhesion molecule (CEACAM) family, a subgroup of IgCAMs [9, 19, 41, 59] (Fig. 2). CEACAMs are surface glycoproteins that are thought to be involved in homotypic and heterotypic cell-cell interactions [20, 45]. They share homologies with carcinoembryonic antigen (CEA), an important tumor marker widely used in the post-surgery surveillance of colon carcinomas. CEACAMs appear to undergo a rapid evolution, since several of the isoforms found in the human genome do not have counterparts in the mouse or rat [21].

Although members of the CEACAM family are expressed by different cell types, the highest levels of CEACAM proteins are present on granulocytes and on epithelial cells, where they are often found on the apical surface [45]. In addition, CEACAM expression can be up-regulated on certain cell types such as endothelial cells or T cells by exposure to pro-inflammatory cytokines or LPS of gram-negative bacteria [6, 42]. Multiple members of the CEACAM family can be expressed by human cells with CEA, CEACAM-1, -3 and -6 serving as receptors for the majority of the characterized neisserial Opa proteins.

Association of Opa_{52}-expressing bacteria with CEACAMs on human phagocytes induces an intracellular signaling cascade that ultimately results in the opsonin-independent uptake of the microorganisms [22] (Fig. 2). A signaling role for CEACAMs has also been

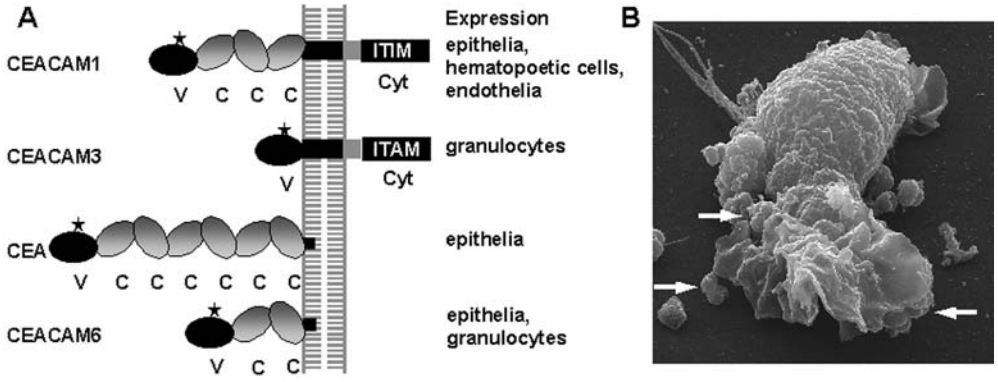

Fig. 2. **A** Schematic representation of human CEACAMs that serve as cellular receptors for Opa proteins of pathogenic *Neisseriae*. CEACAM-1, -3, -6, and CEA are characterized by a single N-terminal v-type Ig domain (*V*; *black*) and a variable number of C2-type Ig domains (*C*; *shaded*). Their N-terminal domain is recognized by Opa_{52}-type Opa proteins (marked by *stars*). CEACAMs can be expressed as transmembrane proteins (CEACAM-1 and -3) or attached to the membrane via glycosylphosphatidylinositol anchors (CEACAM-6 and CEA). The sequence motifs in the cytoplasmic tails (*cyt*) of CEACAM-1 and CEACAM-3 are reminiscent of ITIM and ITAM motifs, respectively. **B** Scanning electron micrograph showing opsonin-independent, CEACAM-mediated uptake of Opa_{52}-expressing gonococci (*white arrows*) by a human phagocytic cell (*CEA* carcinoembryonic antigen, *CEACAM* CEA-related cell adhesion molecule, *ITIM* immunoreceptor tyrosine-based inhibition motif, *ITAM* immunoreceptor tyrosine-based activation motif)

proposed in other systems. Interestingly, of the CEACAM proteins recognized by Opa proteins, only splice variants of CEACAM-1 and -3 possess cytoplasmic domains, whereas CEA and CEACAM-6 are attached to the membrane via a GPI anchor. In addition, the cytoplasmic domains of CEACAM-1 and CEACAM-3 show considerable differences in their primary structure. Specifically, CEACAM-1 comprises amino acid sequences in its intracellular domain that are reminiscent of ITIMs, whereas the CEACAM-3 cytoplasmic tail contains an ITAM. Accordingly, it has been speculated that the ITIM motif of CEACAM-1 contributes to a negative signal. Indeed, expression of the CEACAM-1 cytoplasmic domain fused to the FcγRIIB receptor in chicken B cells can block calcium influx upon cell stimulation [10] and CEACAM-1 stimulation in human T cells impairs cell activation and proliferation [6]. CEACAM-1 has also been shown to associate with SHP-1, a tyrosine phosphatase implicated in negative signaling, and this association was dependent upon the integrity of the ITIM motif [4]. However, recruitment of SHP-1 to this receptor during *N. gonorrhoeae* infection of human phagocytes down-regulates the phosphatase activity of this enzyme in an Opa-protein-dependent manner [23]. Although the ITIM-containing isoform is the major CEACAM-1 isoform expressed on epithelial cells and phagocytes, the functional role of CEACAM-1 and its ITIM motif during the process of neisserial infection and the potential contributions of other Opa-binding CEACAMs are still debated.

In an in vitro model of transcytosis, using a polarized human epithelial cell line derived from colon carcinoma cells, it was shown that Opa_{52}-type adhesins mediate increased transcytosis of gonococci through a confluent, tight-junctions-forming cell layer [60]. As expression of CEACAMs can be induced also in ovarian epithelial cells and endothelial cells by gonococci or lipopolysaccharide [42, 43], it can be speculated that expression of Opa_{52}-type adhesins might allow pathogenic *Neisseriae* to enter host cells and gain access to deeper tissue layers or allow transcytosis in and out of the blood stream. Interestingly, CEACAMs are also recognized by adhesins of other pathogenic bacteria that, like meningococci and gonococci, have exclusively adapted to the human as their sole natural host [27], suggesting a role for this particular IgCAM receptor family in the course of infectious disease in humans. Therefore, more basic information about the biology of CEACAMs in human cells is warranted.

Perspective

The above examples do not represent a complete list of pathogens engaging cell adhesion receptors. Indeed, as we learn more about the intricate interplay at the prokaryote-eukaryote-interface it is becoming evident that binding of cell adhesion receptors is the rule and not the exemption. In addition to the above named examples, cell adhesion receptors seem to play a role in the adhesion and/or invasion of *Shigella flexneri* (employs the hyaluronate receptor CD44 [56]), Group A *Streptococcus pyogenes* (exploits host cell integrins via fibronectin [40, 46]), *E. coli* K1 (invasion of brain microvascular endothelial cells depends on FAK [49]), pathogenic *Ehrlichia spec.* HGE (attaches to the P-selectin glycoprotein ligand-1 (PSGL-1) [26]), *Neisseria gonorrhoeae* (attaches to syndecans [14]), and *Porphyromonas gingivalis* (employs β1 integrins for invasion [62]).

The widespread use of cellular adhesion receptors as entry ports for a range of microorganisms makes it important to note that adhesion receptors are usually not involved in uptake of particulate material from the extracellular space. However, the bacteria binding to

these receptors seem to exploit the linkage to the cellular actin cytoskeleton that these receptors provide to gain control of actin cytoskeleton dynamics (see Fig. 1). The prominent role the plasticity of the actin cytoskeleton plays for the internalization process is illustrated by the essential role of actin polymerization in all of the discussed examples. Nevertheless, it is becoming evident that binding of pathogenic bacteria to these cell adhesion molecules will not only induce the internalization process, but will also modulate additional signals emanating from these receptors. Although signals from cell adhesion receptors often are tightly linked to their structural role with regard to cell shape and motility, they also have a much broader implication by influencing gene expression, the survival and proliferation of the cell as well as tissue architecture and the integrity of the organism. The continued study of the bacteria-receptor interaction will not only yield surprising insight into the intimate relationship between pathogens and their host cells, but will also open up new windows to learn about the signaling capacity and physiological functions of cell adhesion receptors.

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